

2. Overview of the Amendments

Claims 31, 32, 34-63, 80, and 81 have been amended to remove the term "homologous." Accordingly, no new matter has been added by way of this amendment, and the entry thereof is respectfully requested.

3. The Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 31-81 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention.

Absolute specificity and precision are not required in the claims. Claims need only reasonably apprise a person having ordinary skill in the art as to their scope.

Hybritech Inc., v. Monoclonal Antibodies, Inc., 231 USPQ 81, Fed. Cir. 1986. The court has consistently stated that claim language must be read in light of prior art and teachings of the specification. Definiteness of language employed in the claims must be analyzed, not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing an ordinary level of skill in the art. Claims may appear indefinite when read in a vacuum, but may be definite upon reading the specification or prior art teachings. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

The Examiner has objected to use of the term "homologous" in reference to nucleic acid or amino acid sequences. Claims 31, 34-63, 80, and 81 recite the term "homologous." The applicants disagree with the Examiner's

position that the term "homologous" renders the claims indefinite. "Homology" is defined in the specification (for example, on pages 16-17, bridging paragraph). Further, methods for determining homology (for example, page 11, lines 29-34) and degrees of homology (for example, page 17, lines 3-7) are taught in the specification. In order to advance prosecution, however, applicants have amended the claims to remove the term "homology."

Accordingly, in view of the above amendments, the teachings of the specification, and the level of ordinary skill in the present art, the applicants submit that the boundaries of the pending claims are capable of being understood by one of ordinary skill in the art. Therefore, withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph, is requested.

4. The Rejections of Claims Under 35 U.S.C. §103(a)

A. First Rejection

The Examiner has rejected claims 31-63, under 35 U.S.C. §103, asserting that the claims are unpatentable over Mehta.

The prior art cited by the Examiner does not teach the elements of the claimed invention. Specifically, (i) Mehta teaches only mouse monoclonal antibodies -- the pending claims are directed to nucleic acid sequences encoding human Fab molecules; (ii) Mehta does not teach Fab molecules of the mouse monoclonal antibodies. Mehta only teaches "monoclonal antibodies or fragments thereof." The only Fab molecules discussed are Fab dimers derived from IgG molecules purified from individuals serapositive for antibodies to HCV proteins (i.e., polyclonal antibodies) (Mehta, col. 11, lines 6-10). Mehta does not teach an isolated nucleic acid molecule encoding any kind of Fab

molecule -- the pending claims are directed to nucleic acid sequences encoding human Fab molecules; and, Mehta does not teach any nucleic acid sequences for the murine monoclonal antibodies, the sequences in the sequence listing represent HCV peptide sequences (see, Mehta, Example 1 for SEQ ID NOS 1-6, and Example 6 for SEQ ID NOS 7-10 -- the pending claims are directed to nucleic acid sequences encoding human Fab molecules.

The Examiner has not addressed the differences between the prior art and the claims at issue (*Graham v. John Deere Co.*, 383 USC 1, 86 S. Ct. 684, 15 L Ed2d 545, 148 USPQ 459, Supreme Court, 1966). All of the limitations presented in the claims must be considered with respect to the prior art. (*In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, Fed. Cir., 1988).

The Examiner asserts "The sequences encoding the mouse monoclonal VH and VL regions, which are inherent to the antibodies of Mehta, are homologous to human monoclonal antibodies specific for HCV E2 (Office action, page 4, lines 8-10)." This is an unsubstantiated assertion presented by the Examiner. The Examiner has provided no basis in the prior art for this assertion. If the Examiner wishes support the assertion in the absence of a prior art reference, then such an assertion should be submitted in the form of an Examiner's affidavit.

When a rejection is based on facts within the personal knowledge of the Examiner, the data should be stated as specifically as possible, and the reference must be supported, when called for by the applicant, by an affidavit from the Examiner (MPEP 706.02(a)). Such an affidavit is subject to contradiction or explanation by the affidavits of the applicant and other persons (37 C.F.R. 1.107).

It is difficult to imagine that the Examiner's assertion is correct in view of the teachings of Andria, et al., (copy enclosed). The reference states "As of yet, the degree of diversity of antibody responses to haptens can not be predicted (page 2614, col. 1, first paragraph after Abstract)." Further, for antibodies raised against a single antigen, **within** a single species (in this case mice were examined) "Analysis of the V regions of 6 mAb selected for their binding to a defined epitope on TMVP revealed that most of the antibodies have very different amino acid sequences at their CDR and throughout their V regions (p2615, col. 2, second full paragraph). Accordingly, it seems unlikely that variation between species (for example, mice and humans) would be any less variable.

In the absence of a teaching in a cited reference or an Examiner's affidavit, the applicants submit that there is no basis to modify the teachings of Mehta along the lines suggested by the Examiner in order to obtain the isolated nucleic acid molecule of the presently claimed invention.

Finally, the Examiner asserts "the antibodies of Mehta are **very useful** (emphasis added), and one would be strongly motivated to sequence those same antibodies for the purpose of recombinant expression, and for purposes of identifying or creating the human equivalent of those same antibodies."

In going from the prior art to the claimed invention, obviousness cannot be based upon what a person skilled in the art might try or might find obvious to try, but rather must consider what the prior art would have led a person skilled in the art to do (*In re Tomlinson*, 150 USPQ 623, CCPA, 1966). Even if the prior art taught the components of the present invention, the cited reference does not provide any teaching or suggestion as to what direction

experimentation should follow for developing the isolated nucleic acid molecules of the present invention. Further, if the monoclonal antibodies of Mehta are "very useful" where is the motivation to perform the modifications suggested by the Examiner? The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990).

In view of the above arguments, the applicant submits that the reference of Mehta does not support a conclusion of obviousness. In the absence of some teaching or suggestion in the cited reference concerning an isolated nucleic acid molecule encoding a human Fab molecule that exhibits immunological binding affinity for a hepatitis C virus E2 antigen, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. Accordingly, for the reasons presented above, the rejection under 35 U.S.C. §103 is inappropriate and withdrawal of the rejection is requested.

B. Second Rejection

The Examiner has rejected claims 31-81, under 35 U.S.C. §103, asserting that the claims are unpatentable over Wong and Mehta, in view of Hoogenboom and Chanock.

Applicants would appreciate clarification of which reference is being used as the primary reference (Wong or Mehta). The shortcomings of Mehta have been addressed above. Wong does not make up for the shortcomings of Mehta. The reference of Wong is a published Abstract dealing with murine monoclonal antibodies to Hepatitis C Virus E2 envelope protein that block HCV penetration into cells.

There is no teaching or suggestion in the abstract concerning an isolated nucleic acid molecule encoding a human Fab molecule that exhibits immunological binding affinity for a hepatitis C virus E2 antigen. The reference of Wong deals primarily with a penetration assay that "should facilitate future studies to determine the mechanism of HCV binding and entry (last sentence of the Abstract)." It is unclear how the Examiner imagines that Wong as a primary reference could be modified to obtain the nucleic acid molecules of the present invention.

Further, it is unclear to the applicants why the Examiner rejected claims 31-63 under 35 U.S.C. §103(a) with Mehta as the sole, cited reference, and then rejected the same group of claims again (included in claims 31-81) with the same primary reference (Mehta) using a series of secondary references to modify the teachings of the primary reference. As discussed below, Mehta can neither stand alone or in combination with the other cited references to provide a reasonable basis for a rejection under 35 U.S.C. §103.

The Examiner relies heavily on prohibited hindsight reconstruction in framing the rejection of the claims. The Examiner first characterizes selected elements of each of the references (Office action, page 4, line 19, to page 5, line 13). However, obviousness cannot be established by combining teachings in the prior art absent some teaching or suggestion in the prior art that the combination be made. *In re Stence*, 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). *In re Newell*, 891 F. 2d 899, 13 USPQ2d 1248 (Fed Cir 1989). In particular, the fact that references can be combined does not make the combination obvious unless the prior art also contains something to suggest the desirability of that

combination (*In re Sernaker*, 702 F.2d 989, 217 USPQ 1, Fed. Cir. 1983).

The Examiner attempts to provide the requisite motivation to combine the disparate elements gleaned from the references. "It would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned and identified sequences encoding human Fab fragments specific for the E2 protein of HCV from a combinatorial library through the methods of Hoogenboom and to have further cloned these sequences into appropriate expression vectors for the purposes of recombinant expression of the Fab fragments as set forth by Chanock (Office action, page 5, lines 14-18)." As the Federal Circuit stated in *In re Newell*, 891 F.2d, 13 USPQ2d 1248 (Fed. Cir. 1989):

"[a] retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination."

Practicing the present invention by a combination of the cited references can be done only by virtue of the Examiner's improper reconstructive hindsight. There is no motivation provided by the prior art to combine the teachings of the prior art in order to obtain an isolated nucleic acid molecule encoding a human Fab molecule that exhibits immunological binding affinity for a hepatitis C virus E2 antigen.

The Examiner goes on to assert "One would have wanted to produce these antibodies because monoclonal antibodies against the E2 protein had been shown by Wong to prevent the penetration of HCV into target cells, and Mehta disclosed that these antibodies would be useful in immunoassays and

diagnostic procedures as a more reliable indication of HCV infection (Office action, pages 5-6, bridging sentence). " First, Wong and Mehta disclose only murine monoclonal antibodies (as discussed above). Second, this assertion is also a conclusion drawn by the Examiner that does not find support in Wong or Mehta. Neither reference suggests that further monoclonal antibodies need to be identified, let alone, that human Fab molecules should be developed. Nor do the references suggest the need for a "more reliable indication of HCV infection" than what has been already taught in the references (i.e., the murine monoclonal antibodies).

In view of the above arguments, the applicant submits that the cited references do not support a conclusion of obviousness. In the absence of some teaching or suggestion in the cited reference concerning an isolated nucleic acid molecule encoding a human Fab molecule that exhibits immunological binding affinity for a hepatitis C virus E2 antigen, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

Accordingly, for the reasons presented above, the rejection under 35 U.S.C. §103 is inappropriate and withdrawal of the rejection is requested.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

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Respectfully submitted,

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enclosure: Andria, M.L., et al., *J. Immunol.* **19**:2614-2619 (1990): "Diverse V_H and V_L Genes Are Used To Produce Antibodies Against A Defined Protein Epitope."

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